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Parasite in the brain: the role of *Toxoplasma gondii* in brain cancer and neuropsychiatric disorders

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Abstract

Toxoplasma gondii (T. gondii) is a protozoan parasite that affects about one-third of the world's human population, frequently creating a dormant presence in the brain. Recent studies have placed growing emphasis on the possible consequences of *T. gondii* infection concerning brain cancer and neuropsychiatric conditions, such as schizophrenia, bipolar disorder, and depression. This review consolidates recent discoveries regarding how *T. gondii* could affect neurological well-being, especially its capacity to modify neurotransmitter pathways, adjust immune reactions, and provoke neuroinflammation. We examine the epidemiological links between *T. gondii* seropositivity and different psychiatric disorders, highlighting the necessity for additional research into the causal mechanisms connecting this parasite to brain pathology. Moreover, we investigate the possibility of *T. gondii* as a co-factor in developing brain tumors, emphasizing its function in immune evasion and modulation of the tumor microenvironment. Grasping these connections is essential for creating focused therapeutic approaches and public health measures designed to reduce the impact of *T. gondii* infection on mental health and neuro-oncology.

Keywords: *Toxoplasma gondii*, Brain cancer, Neuropsychiatric disorders, Neurotransmitter modulation, Neuroinflammation

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Introduction

T. gondii is an intracellular protozoan parasite that is obligatory and has attracted considerable attention because of its common occurrence and possible effects on human health (1). It is estimated that as many as 30% of the worldwide population carries this parasite, frequently without showing any symptoms. Nonetheless, persistent infections can result in significant neurological effects, especially if the immune system is weakened or experiences stress (2). The parasite is mainly spread by ingesting oocysts found in contaminated food or water, along with vertical transmission from mother to fetus or via organ transplantation (3). The central nervous system (CNS) acts as a key reservoir for *T. gondii*, allowing it to create tissue cysts that endure for the lifetime of the host (4). These cysts may reactivate when the immune system is suppressed, resulting in acute toxoplasmosis that can cause serious neurological symptoms like encephalitis or psychological issues (5). The connection between *T. gondii* infection and several neuropsychiatric disorders has been extensively studied, with research showing a notable link between *T. gondii* seropositivity and disorders like schizophrenia, bipolar disorder, and depression (6).

Mechanisms of Neuroinvasion

The processes through which *T. gondii* enters and influences the brain are intricate and varied. Once inside the host's body, *T. gondii* can traverse the blood-brain barrier (BBB), which is a selectively permeable barrier that shields the brain from pathogens and permits the passage of vital nutrients (7). *T. gondii*'s capability to cross this barrier is linked to its distinctive interactions with host cells and its ability to influence host immune responses. Upon entering the CNS, *T. gondii* can trigger notable alterations in neurotransmitter systems, especially those related to dopamine and gamma-aminobutyric acid (GABA) (8). Studies have indicated that infected persons may display changed levels of these neurotransmitters, essential for mood control and cognitive abilities (9). For example, increased dopamine levels have been correlated with behavioral alterations seen in both infected humans and animal models, indicating a possible connection between *T. gondii* infection and psychotic disorders like schizophrenia (10) (Figure 1).

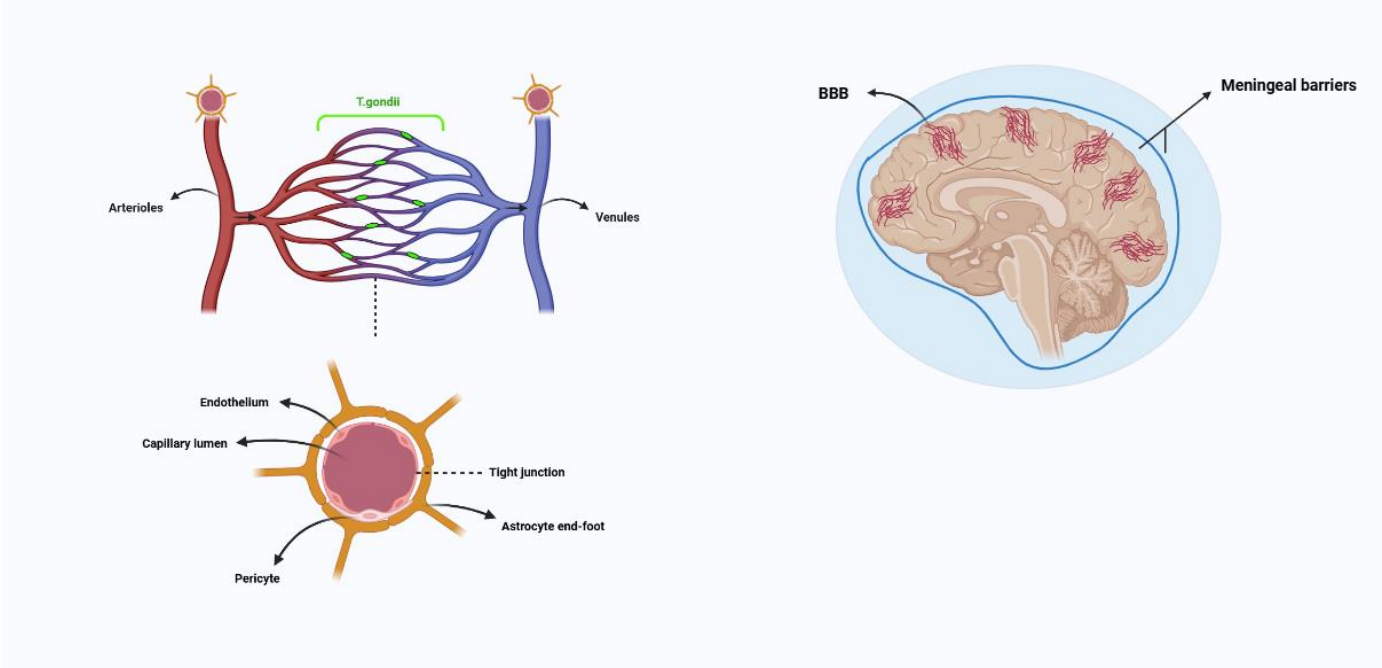

Figure 1. Blood-Brain Barriers and *Toxoplasma gondii* Invasion. This figure illustrates the complex architecture of the blood-brain barrier (BBB) and how the parasite *Toxoplasma gondii* can breach these barriers to gain entry into the central nervous system (CNS).

Epidemiological Evidence

A variety of epidemiological studies have indicated elevated seroprevalence rates of *T. gondii* in individuals with psychiatric disorders when compared to healthy controls (11). For instance, research has shown that individuals with schizophrenia demonstrate seropositivity rates between 50% and over 70%, which is markedly higher than those observed in the general population (12). These results prompt significant inquiries about causality: does infection with *T. gondii* play a role in initiating or worsening psychiatric symptoms? Or do existing psychological conditions make individuals more susceptible to higher infection rates? Although clear causal pathways are still uncertain, it is evident that a strong connection exists between chronic *T. gondii* infection and multiple neuropsychiatric conditions (13) (Figure 2).

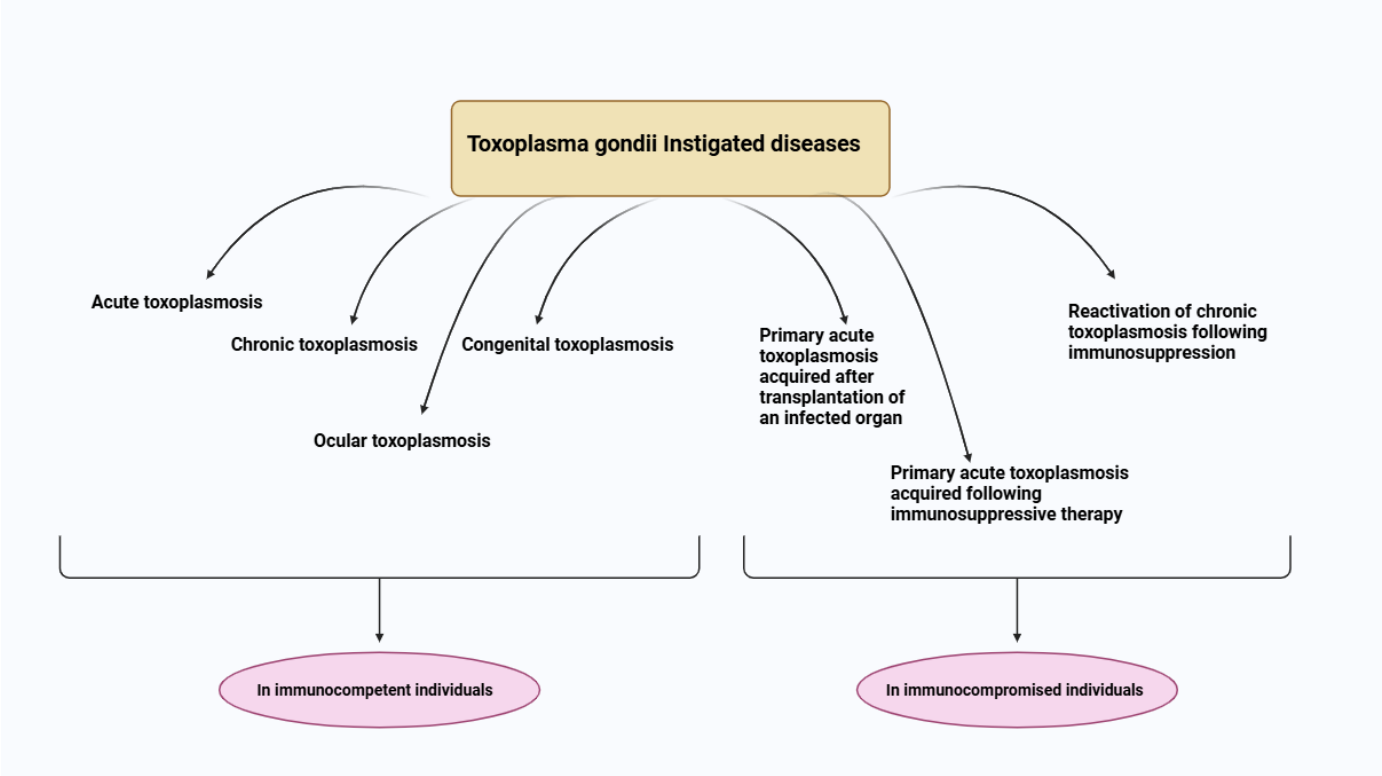

Figure 2. *Toxoplasma gondii*-Instigated Diseases. This figure illustrates the various clinical presentations of toxoplasmosis, a parasitic disease caused by *Toxoplasma gondii*, categorized based on the host's immune status.

Neuroinflammation and Immune Response

The immune reaction triggered by *T. gondii* infection is crucial for its effects on brain health. Infected persons frequently show indications of neuroinflammation marked by elevated levels of pro-inflammatory cytokines and stimulation of glial cells in the CNS (14, 15). This inflammatory reaction may result in neuronal injury and add to the cognitive impairments seen in those impacted. Additionally, persistent inflammation might create conditions that promote tumor formation in the brain (16). Recent studies indicate that ongoing inflammation due to long-term infections like those from *T. gondii* may facilitate tumor growth through processes including immune evasion and changes in local tissue microenvironments (17). This suggests a possible connection between long-term parasitic infections and brain cancer (18, 19) (Figure 3).

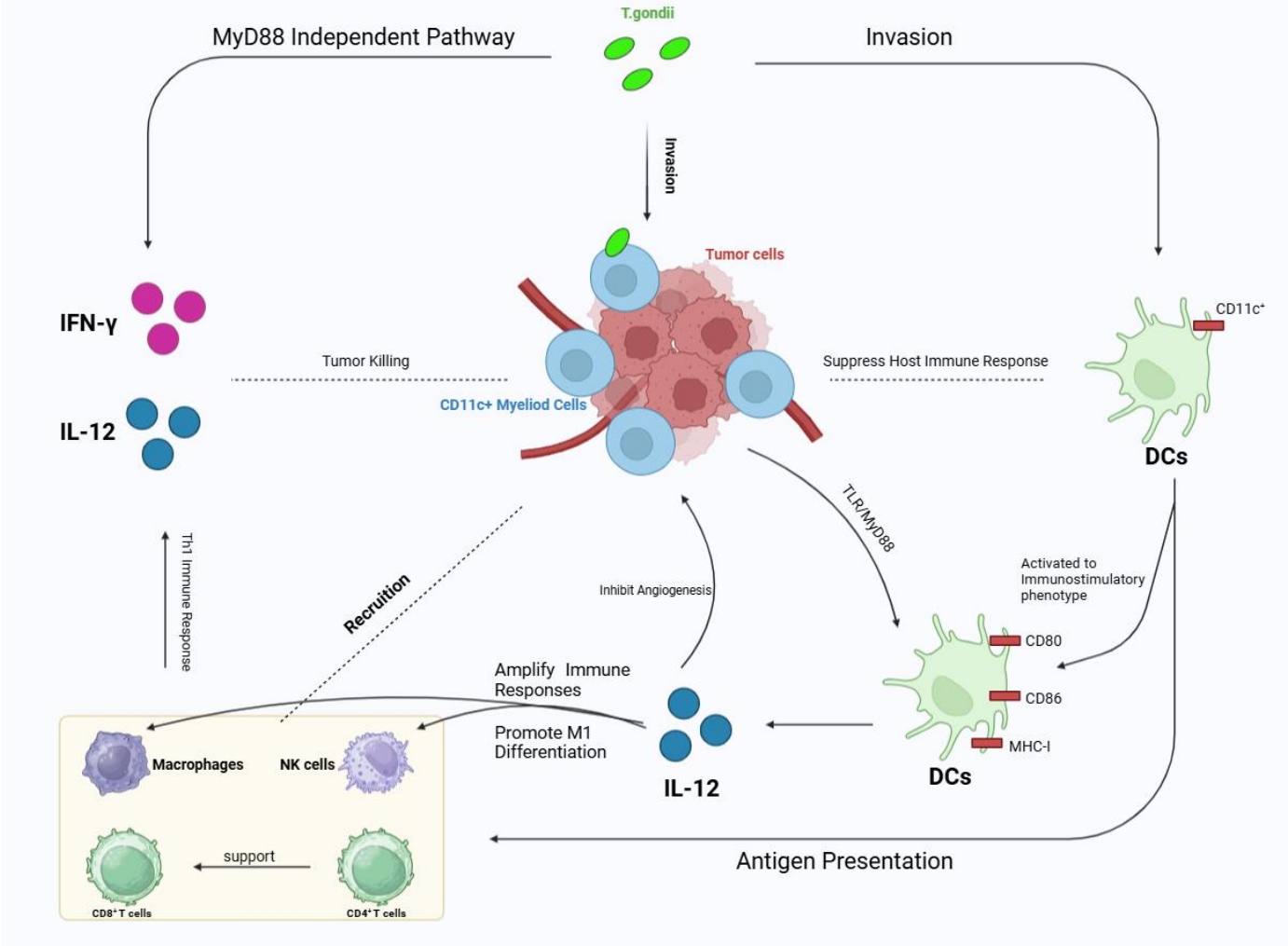

Figure 3. *Toxoplasma gondii*-induced Immune Response and Its Impact on Tumor Cells. This figure illustrates the complex interplay between *Toxoplasma gondii* (*T. gondii*) infection, the host immune response, and tumor cells. The shapes represent different types of cells and molecules involved in this interaction. Arrows indicate *T. gondii* invading both tumor cells and DCs. *T. gondii* infection activates DCs, leading to the upregulation of co-stimulatory molecules (CD80, CD86), enhancing their ability to stimulate T-cell responses. *T. gondii* infection stimulates DCs to produce IL-12, a cytokine that promotes Th1 immune responses, including the activation of CD8+ T cells and NK cells.

Toxoplasma gondii and Neuropsychiatric Disorders

Toxoplasma gondii, a prevalent neurotropic parasite, has become more associated with several neuropsychiatric disorders in humans. These links encompass schizophrenia, Alzheimer's disease, and Parkinson's disease, although the precise pathogenic mechanisms are still not fully understood. *T. gondii* can remain in the brain as tissue cysts, requiring an ongoing immune response to stop the reactivation of the infection (20, 21). Chronic infection is especially worrying, as evidence indicates it can result in neurodegeneration in certain areas of the brain, like the anterior cingulate cortex and somatomotor cortex, impacting both glutamatergic and GABAergic neurons (22, 23). Changes in behavior among infected individuals may be partially linked to variations in neurotransmitter levels, especially dopamine. Research has shown that *T. gondii* infection is linked to heightened dopamine metabolism, a component associated with the onset of schizophrenia (20). This connection is additionally reinforced by evidence indicating that those with *T. gondii* antibodies might display elevated rates of aggression, impulsivity, and possibly heightened risks for suicide and traffic accidents, hinting at wider behavioral consequences (24, 25). The neuroinflammatory reaction initiated by *T. gondii* infection significantly impacts neurobiology, possibly resulting in alterations in neurotransmitter receptor quantities and synaptic connections (26). This

inflammation may play a role in the development and progression of multiple neurodegenerative diseases, since long-term *T. gondii* infection might encourage neurodegeneration and neurocognitive irregularities (6, 23, 27). Studies persist in investigating the intricate connection between *T. gondii* infection and neuropsychiatric effects, which affects our comprehension of the mechanisms behind behavioral alterations and the possibilities for preventive measures (28).

Conclusion

The relationship between *Toxoplasma gondii* (*T. gondii*) infection and brain tumors has garnered increasing attention in the scientific community, particularly regarding its implications for public health and cancer prevention strategies. This study demonstrates a significant association between *T. gondii* infection and various types of brain tumors, including gliomas and meningiomas. The findings underscore the need for further research to elucidate this association's underlying mechanisms and explore potential therapeutic avenues. Recent studies consistently show a higher prevalence of *T. gondii* seropositivity among patients with brain tumors compared to healthy individuals. For instance, a systematic review and meta-analysis identified an overall odds ratio (OR) of 1.96 for the link between *T. gondii* infection and brain tumors, with specific ORs of 1.64 for gliomas and 2.30 for meningiomas. These findings suggest that individuals exposed to *T. gondii* may have approximately double the risk of developing brain tumors, highlighting the need for further investigation. One proposed mechanism by which this parasite may contribute to tumorigenesis is its ability to modulate the tumor microenvironment. The parasite's invasion and persistence in the central nervous system could lead to chronic inflammation, which may promote tumor growth. Research indicates that *T. gondii* can increase tumor cell proliferation by downregulating antitumor genes such as PTEN and FoxO1. This suggests that *T. gondii* not only affects immune responses but also alters critical signaling pathways involved in cell growth and survival.

Future Research Directions

While existing studies provide compelling evidence of an association between *T. gondii* infection and brain tumors, several critical gaps remain in our understanding (29, 30). First, it is essential to establish the causal relationship between infection and tumor development through well-designed cohort studies that control for confounding factors such as age, immune status, and other environmental exposures. Additionally, we need to determine whether the development of tumors creates a favorable environment for parasite growth or if pre-existing tumors contribute to this process. Moreover, it is crucial to investigate the biological mechanisms underlying this association. Future research should focus on elucidating how host immune responses are altered and how these changes modulate cellular pathways involved in oncogenesis. Understanding these mechanisms could lead to novel therapeutic strategies that target *T. gondii* as a potential risk factor for brain tumors (31, 32).

Implications for Public Health

The implications of these findings extend beyond academic interest and raise important public health considerations. With *T. gondii* infections estimated to affect around one-third of the global population, there is an urgent need for public health initiatives aimed at reducing exposure to this parasite (33, 34). Improved cooking and sanitation practices can help lower transmission risks. Additionally, screening programs targeting high-risk populations can facilitate early detection and intervention for those with chronic infections. Understanding the link between infectious agents like *T. gondii* and cancer can strengthen our cancer prevention efforts by identifying modifiable risk factors (35, 36). In conclusion, the evidence connecting *Toxoplasma gondii* infection to an increased risk of brain tumors is compelling, but further exploration is necessary to fully comprehend its implications for cancer development and public health (37). The relationship among chronic infection, immune modulation, and tumor growth presents a complex landscape that requires interdisciplinary research efforts. By clarifying these connections, we can enhance prevention strategies and potentially develop targeted therapies that address both the management of infectious diseases and cancer treatment.

Author contribution

PR was involved in the investigation, methodology, and writing the primary draft of the manuscript, **MEB** was involved as a supervisor in all sections of the manuscript including conceptualization, writing, reviewing and also editing. All the authors studied the final version of the paper and acknowledged it.

Conflict of interest

There is no Conflicts of interest/competing interests.

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References

1. Zhao X-Y, Ewald SE. The molecular biology and immune control of chronic *Toxoplasma gondii* infection. The Journal of clinical investigation. 2020;130(7):3370-80.

2. Del Pino LEB, Zanón-Moreno V. Systematic Review on the Relationship between Toxoplasmosis and Mental Disorders. Actas Españolas de Psiquiatría. 2024;52(2):149.

3. de Haan L, et al. Association of *Toxoplasma gondii* seropositivity with cognitive function in healthy people: A systematic review and meta-analysis. JAMA psychiatry. 2021;78(10):1103-12.

4. Oncu-Oner T, Can S. Meta-analysis of the relationship between *Toxoplasma gondii* and schizophrenia. Annals of parasitology. 2022;68(1).

5. Cossu G, et al. Association between toxoplasmosis and bipolar disorder: A systematic review and meta-analysis. Journal of Psychiatric Research. 2022;153:284-91.

6. Ortiz-Guerrero G, et al. Pathophysiological mechanisms of cognitive impairment and neurodegeneration by *Toxoplasma gondii* infection. Brain sciences. 2020;10(6):369.

7. Pittman KJ, Knoll LJ. Long-term relationships: the complicated interplay between the host and the developmental stages of *Toxoplasma gondii* during acute and chronic infections. Microbiology and molecular biology reviews. 2015;79(4):387-401.

8. Wang M, Jiang W. Virulence evolution of *Toxoplasma gondii* within a multi-host system. Evolutionary Applications. 2023;16(3):721-37.

9. Ihara F, et al. Changes in neurotransmitter levels and expression of immediate early genes in brain of mice infected with Neospora caninum. Sci Rep. 2016;6(1):23052.

10. Yang L, et al. *Toxoplasma gondii* infection positively associated with schizophrenia: Evidences from UK Biobank cohort and case-controlled studies. Journal of Psychiatric Research. 2024;175:243-50.

11. Maisarah A, et al. Association between infection with *Toxoplasma gondii* and psychiatric disorders. Folia Parasitologica. 2022;69:1-10.

12. Ademe M, et al. Is latent *Toxoplasma gondii* infection associated with the occurrence of schizophrenia? A case-control study. PLoS One. 2022;17(6):e0270377.

13. Li Y, et al. Chronic *Toxoplasma gondii* infection induces anti-N-methyl-d-aspartate receptor autoantibodies and associated behavioral changes and neuropathology. Infection and immunity. 2018;86(10):10.1128/iai. 00398-18.

14. Steffen J, et al. Type 1 innate lymphoid cells regulate the onset of *Toxoplasma gondii*-induced neuroinflammation. Cell Reports. 2022;38(13).

15. Laing C, et al. Noradrenergic signaling and neuroinflammation crosstalk regulate *Toxoplasma gondii*-induced behavioral changes. Trends in Immunology. 2020;41(12):1072-82.

16. Tu X-k, et al. GLP-1R agonist liraglutide attenuates inflammatory reaction and neuronal apoptosis and reduces early brain injury after subarachnoid hemorrhage in rats. Inflammation. 2021;44:397-406.

17. Chen L, et al. Adenosine, bridging chronic inflammation and tumor growth. Frontiers in Immunology. 2023;14:1258637.

18. Thirugnanam S, et al. Possible role of *Toxoplasma gondii* in brain cancer through modulation of host microRNAs. Infectious agents and cancer. 2013;8:1-6.

19. Jung YY, et al. Pyrimethamine modulates interplay between apoptosis and autophagy in chronic myelogenous leukemia cells. International Journal of Molecular Sciences. 2021;22(15):8147.

20. Matta SK, et al. *Toxoplasma gondii* infection and its implications within the central nervous system. Nature Reviews Microbiology. 2021;19(7):467-80.

21. Ammar AM, et al. Correlation between toxoplasmosis and schizophrenia in Egyptian patients and its impact on dopamine serum levels. Acta Tropica. 2024;256:107263.

22. Omidian M, et al. Acute toxoplasmosis can increase serum dopamine level. Journal of Parasitic Diseases. 2022:1-6.

23. Li Y, et al. Persistent Toxoplasma Infection of the Brain Induced Neurodegeneration Associated with Activation of Complement and Microglia. Infect Immun. 2019;87(8).

24. Abdulai-Saiku S, et al. Behavioral manipulation by *Toxoplasma gondii*: Does brain residence matter? Trends in parasitology. 2021;37(5):381-90.

25. Sugden K, et al. Is *Toxoplasma gondii* infection related to brain and behavior impairments in humans? Evidence from a population-representative birth cohort. PLoS One. 2016;11(2):e0148435.

26. Webster JP, et al. *Toxoplasma gondii* infection, from predation to schizophrenia: can animal behaviour help us understand human behaviour? J Exp Biol. 2013;216(1):99-112.

27. Mirzaeipour M, et al. Evaluation of the tyrosine and dopamine serum levels in experimental infected BALB/c mice with chronic toxoplasmosis. Journal of Parasitology Research. 2021;2021(1):5511516.

28. Virus MA, et al. Neurological and neurobehavioral disorders associated with *Toxoplasma gondii* infection in humans. Journal of parasitology research. 2021;2021(1):6634807.

29. Erickson LD, et al. Association between *Toxoplasma gondii* seropositivity and serointensity and brain volume in adults: A cross-sectional study. PLoS One. 2021;16(2):e0245994.

30. Jung B-K, et al. Exosomal miRNA-21 from *Toxoplasma gondii*-infected microglial cells induces the growth of U87 glioma cells by inhibiting tumor suppressor genes. Sci Rep. 2022;12(1):16450.

31. Asgari Q, et al. *Toxoplasma gondii* infection in patients with brain tumors in Southern Iran: a case-control study. Journal of Parasitic Diseases. 2023;47(2):291-6.

32. Alim M, et al. Seroprevalence of *Toxoplasma gondii* in patients receiving cancer treatment. Cumhuriyet Medical Journal. 2018;40(1):19-24.

33. Lima TS, Lodoen MB. Mechanisms of human innate immune evasion by *Toxoplasma gondii*. Frontiers in cellular and infection microbiology. 2019;9:103.

34. Teimouri A, et al. Role of *Toxoplasma gondii* IgG avidity testing in discriminating between acute and chronic toxoplasmosis in pregnancy. Journal of clinical microbiology. 2020;58(9):10.1128/jcm. 00505-20.

35. Egan KM, et al. Prospective investigation of polyomavirus infection and the risk of adult glioma. Sci Rep. 2021;11(1):9642.

36. Mao F, et al. Seroprevalence and risk factors of *Toxoplasma gondii* infection among high-risk populations in Jiangsu Province, Eastern China. Frontiers in Cellular and Infection Microbiology. 2021;11:783654.

37. Rostami A, et al. Does latent Toxoplasma infection have a protective effect against developing multiple sclerosis? Evidence from an updated meta-analysis. Transactions of The Royal Society of Tropical Medicine and Hygiene. 2022;116(11):996-1006.